REMARKS

Reconsideration is respectfully requested in view of the remarks which follow.

The claims presently pending in the application are 7 – 13, inclusive.

Claims 7 – 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Di Schiena (EP 0444492) in view of Saxen at al. (Oral Surgical Oral Medical Oral Pathology Oral Radiology Endod). This rejection is respectfully traversed.

It should be noted that when pages of the publication are referenced hereinafter it is to the International Application n. WO 2005/000321.

The Examiner states that Di Schiena does not exemplify the treatment of recurrent oral aphthous ulcers, describing only "*pharmaceutical compositions comprising 0.2 to 10% sodium hyaluronate having molecular weight between 800,000 – 4,000,000*". Furthermore, the Examiner states that "*Saxen et al. teach that recurrent aphthous ulcers are a common disorder…A reduction in pain was observed 10 minutes after application with no significant difference between the three topical agents [see abstract]. Ulcers were smaller after treatment with HA [page 359, Table 1]*". The Examiner thus concludes that, "*it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Di Schiena's composition for the treatment of recurrent aphthous ulcers*".

In responding to the Applicants' previous arguments based upon improper hindsight reasoning, the Examiner states that "*it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.*"

As it will be shown hereafter, the technical information used by the Examiner in order to justify and support her reasoning for concluding that obviousness is present is, in fact, not derivable from knowledge which was within the level of ordinary skill at the time the claimed invention was made, but, contrarily, represents knowledge which was improperly construed by modifying the content of the prior art with a preordained mindset of reproducing the teaching which is recited in claim 1.

First of all, the Examiner states: "*Saxen teaches that topical application of HA provides immediate pain relief for recurrent aphthous ulcers, even in absence of other active ingredients. Although HA was inferior to HA/diclofenac after 1 hour, immediate pain relief is clearly taught*". This is ***unquestionably wrong***, because Saxen teaches in Table II at 1 hour that the group receiving HA/diclofenac was extremely better, from a VAS score of 2.25 (baseline) to 0.798 (difference: 1.452), than the group receiving only HA, from a VAS score of 2.89 to 2.028 (difference: 0.862). Furthermore, Saxen also teaches that lidocaine at 1 hour went from a VAS score of 2.71 to 1.683 (difference: 1.027) was better than the group receiving only HA (from VAS score 2.89 to 2.028 (difference: 0.862)). Therefore, the skilled person in view of the data at 1 hour is only informed or taught to use for immediate relief Diclofenac/HA, or alternatively, lidocaine, both showing so much better results than the group receiving only HA. Furthermore, the skilled person engaged in research for the treatment of ROAU, in view of the data shown in Table II, would never even have tried to use HA because at 2 hours from the initial treatment the group treated ***solely with HA*** gave a ***higher VAS score*** which was higher ***than at 1 hour***, specifically 2.190, therefore typifying a **worsening** situation. Thus, the skilled person would have been certain, beyond any doubt, that the treatment of ROAU with HA was not possible.

As a matter of fact, this is clearly stated by Saxen himself, as follows: " A 35% to 52% pain reduction ($p<0.01$) was reported 2 to 6 hours after the application of diclofenac in hyaluronan, while **hyaluronan gel alone** and viscous lidocaine **FAILED** to produce significant VAS reduction".

Therefore, it is evident that only by purposely extrapolating the HA data of Table II with the aim of reproducing claim 1, without considering or in fact ignoring what is stated by Saxen and what is really shown by Saxen, can the obviousness reasoning of the Examiner be understood.

In responding to the Applicant's arguments, the Examiner also stated "*a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiment*".

In this case, the group treated with only HA cannot "*reasonably*" be deemed a suggestion, because in this group there is no treatment of ROAU. In view of the reported results and the conclusions of Saxen's article, the skilled person would not have reasonably tried to treat ROAU patients because from the available evidence he would have reasoned that no results can be achieved. The group treated with only HA cannot be considered a "nonpreferred embodiment", but at most "a comparison group", in order to show the better results of Diclofenac/HA with respect to only HA and lidocaine in the treatment of ROAU. The values extrapolated by the Examiner cannot be reasonably deemed a suggested result to a physician seeking to treat ROAU patients, because no treatment of ROAU is disclosed.

In order to support her reasoning, the Examiner refers to Table 1 of Saxen, affirming "*Table 1 does show a decrease in lesion size after treatment. Pretreatment lesion size was 5.0 (3-9) and posttreatment lesion size was 4.58 (0-6). Although Saxen states that the change is not significant, Table 1 clearly teaches that there was a reduction in lesion size. The maximum lesion size went from 9 to 6, a 30% reduction, and the smallest ulcer size went from 3 to 0.*".

First of all, Applicant wishes to draw the attention of the Examiner to the fact that in Table 1 demographic characteristics of the treatment groups are shown. As is well known to those of ordinary skill in the art, the demographic characterization is carried out in a study only with the purpose of guaranteeing the equivalence of the treated groups. The demographic characterization, in accordance with the objective, is necessary in order to be able to state that the three (3) tested groups show similar results in order to

guarantee that the study is correctly carried out. In this case the objective is stated after the title, "*Objectives: the purpose of this study was to test the hypothesis that topically applied 3%diclofenac in 2.5% hyaluronan reduces aphthous ulcer pain*". Therefore, the objective is to study the reduction of the pain from aphthous ulcers. Three (3) groups of patients were prepared and in accordance with a certified study the demographic characteristics of all the three (3) groups were evaluated. No significant results are reported in Table 1.

The fact that the lesion sizes for the three (3) groups are not a significant result in the study, would immediately be clear to the person of ordinary skill by noting the column of p values in Table 1. As is well-known, the p value is the statistical significance of a value. As it is also known, a value is deemed significant if p is below 0.05 or highly significant if it is below 0.01.

In the case of the lesion size (pretreatment), the p value is 0.91 and the lesion size (posttreatment) is 0.32, that means that they are not significant values in the study. On the other hand, Saxen states that Table 1 only has the purpose of giving the demographic characteristic in order to show the equivalence of the groups and not to give values which would be considered by the skilled person as the basis for medical treatment. This is also confirmed by Table II, for which the significance of p is below 0.05.

Therefore, in the field of medicine, wherein the treatment decision is the physician's responsibility, the skilled person would never have considered these data as having a meaning other than what is stated in the article.

Even if the Applicant, hypothetically, were to go against or counter to the well-known rules of reading data in a table, the reasoning advanced by the Examiner is deeply wrong and seriously flawed.

The Examiner states, "*The maximum lesion size went from 9 to 6, a 30% reduction, and the smallest ulcer size went from 3 to 0.*" [emphasis added]. The lesion size pretreatment value of 5.0 for the HA group indicates in parenthesis "9-3". This means that in the group formed by 20 patients, one has 9 and one has 3. In order to have

a medium value of 5.00, it's clear that the majority of the 20 patients has a value closer to 3, so as to arrive at a balance of 5. The lesion size posttreatment value of 4.58 for the HA group in parenthesis indicated "0-6". This means that in the group formed by 20 patients, one patient has 0 and one has 6. In order to have a medium value of 5.00, it's clear that almost all of the remaining 18 patients shows a value close to 6, so as to balance the medium value to 5. Therefore, no logical basis for a 30% reduction can be recognized. Clearly, the 30% value is a reconstruction by the Examiner without any logical, statistical, mathematical basis or any other type of reasoning based on the reported data.

On the other hand, and this is confirmed by Saxen himself, who states "No significant change in ulcer diameter or clinical appearance of the ulcer was observed throughout the trial…".

Furthermore, the sole results reported by Saxen in the treatment of RAOU is the pain relief as clearly stated in the objectives, having no relevance to the demographic characteristics of lesion sizes of the groups, but being significantly relevant to the reported VAS scores of the patients, independently of the lesion size.

Thus, one of ordinary skill in the art reading this document is no doubt aware of the fact that Saxen et al. only refer to the therapeutic action of diclofenac in hyaluronan in the treatment of recurrent aphthous ulcers and that "hyaluronan gel alone and viscous lidocaine FAILED to produce significant VAS reduction",….

From the above essential features, it is evident that the skilled person is taught to use diclofenac as the only available treatment in recurrent aphthous ulcers.

Now, Applicant wonders how would the skilled person be motivated to modify the teaching of Saxen et al., in the direction of the current invention, thus combining it with Di Schiena's product, when all of the data in reducing the pain in recurrent aphthous ulcers by Saxen et al teach away from the use of hyaluronan.

Applicant is convinced beyond any doubt that the Examiner came to her conclusions on the basis of a further hindsight, while it is clear that the skilled person would have had no reason to even attempt to combine Di Schiena with Saxen et al. in

order to arrive at the claimed invention since the futility of such an attempt would have been apparent on its face..

In the Experiment described in Annex 1, the Nolan et al article in J. of Oral Pathology (2006) filed with the Amendment of September 26, 2008, the following results were achieved by the authors:

(a) a statistically significant ($p=0.04$) reduction of ulcers on day 5 in patients treated with HA(1.65 ± 0.25) , when compared to the placebo group (2.4 ± 0.26) (see table 2);

(b) a statistically significant ($p=0.047$), reduction on day 4 of new ulcer occurrence in patients treated with HA(2), when compared to the placebo group (10) (see table 4); and,

(c) a statistically significant ($P<0.001$) increase of patients free from ulcers on day 7 in patients treated with HA (24), when compared with patients treated with placebo (19) (see table 3).

These results confirm without any doubt that the sole active ingredient hyaluronic acid as per claim 1 can be used successfully in the treatment of ROAU and this is most definitely an unexpected result achieved by the claimed invention, particularly in view of the directly contrary teaching of Saxen et al.

For all the above reasons, Applicant is firmly convinced that the invention, as set forth in the currently amended claims, clearly distinguishes over the combination of Di Schiena in view of Saxen. Since the Examiner has failed to establish a case of ***prima facie*** obviousness by a preponderance of the evidence, withdrawal of the § 103(a) rejection is respectfully urged.

The issuance of a Notice of Allowance is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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